REMARKS/ARGUMENTS

In response to the Office Action of January 12, 2005, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claim Status/Support for Amendments

Claims 1, 39 and 44-46 have been amended. Claims 2-38 were cancelled in a previous response (filed on December 10, 2004). Claims 39-46 are withdrawn from consideration. It is understood that claims 39-46, drawn to the non-elected invention, will remain pending, albeit withdrawn from prosecution on the merits at this time. If the examined claim of the Group I invention is deemed to be allowable, rejoinder of the remaining claims (39-46) in accordance with the decision in *In re Ochiai* is respectfully requested; since the remaining claims (39-46) are limited to the use of the biopolymer marker of claim 1 (the examined claim of the elected Group I invention).

Claim 1 is under examination. Claims 1 and 39-46 remain pending in the instant application.

No new matter has been added by the amendments to the specification made herein.

The title of the invention has been amended to clearly

indicate the invention to which the pending claims are drawn.

In the "Background of the Invention" section a punctuation error was corrected at page 1, line 23.

The description of the reference at page 5 has been amended to correct a typographical error in the international application number. The corresponding international publication number has also been added.

The "Description of the Figures" section has been amended to add sequence identification numbers and to clearly indicate that Figures 2-4 and 6 show the mass spectrum profiles of the disclosed biopolymer markers.

Several protocols at pages 40-45 have been amended to properly identify trademark names (SEPHAROSE, TRITON, TRIS and EPPENDORF). The protocol titles at page 41 (line 12), page 42 (lines 3 and 18) and page 43 (lines 9 and 22) were underlined in the original disclosure and do not indicate amended text. The HiQ Anion Exchnage Mini Column Protocol was also amended to correct a typographical error (fractions replaced fraction).

In the "Detailed Description" section, the term "cerebrospinal fluid" has been added to define the abbreviation "CSF" at page 49, line 17 in order to provide explicit support for cerebrospinal fluid as recited in claim 41. "CSF" is a well known abbreviation for cerebrospinal fluid in the biochemical art. A typographical

error within the same paragraph has also been amended (skill replaced skilled).

The abstract has been amended to remove the legal phraseology ("said").

No new matter has been added by the amendments to the claims made herein.

Claim 1 has been amended to explicitly claim the biopolymer marker (SEQ ID NO:3). The term "biopolymer marker" is used throughout the specification as originally filed, see, for example, page 1, line 8.

Claim 39 has been amended to clearly disclose the relationship between the presence of the claimed biopolymer marker (SEQ ID NO:3) and insulin resistance. Claim 39 has also been amended to explicitly indicate how the presence of the claimed biopolymer marker is determined from mass spectrum profiles. The changes to claim 39 find basis throughout the specification as originally filed, see, for example, page 35, lines 14-18, page 46, lines 10-18 and Figures 1, 4 and 5.

Claim 44 has been amended to correspond with the biopolymer marker of claim 1 (as amended herein). Support for various types of kits can be found in the original disclosure, see for example, page 36, lines 9-12 and page 47, line 15 to page 49, line 1. Claim 44 was also amended to correct a grammatical error(an replaced

and).

Claims 45 and 46 have been amended to provide proper antecedent basis for the term "kit" in claim 44 (as amended herein).

Restriction

The Examiner has determined that the requirement for restriction is still proper and therefore has made the requirement final.

Applicants have claimed the biopolymer markers (SEQ ID NOS:1-4)in a Markush-type grouping indicating that SEQ ID NOS:1-4 are alternatively usable (MPEP 803.02). In contrast to Applicants' presentation of SEQ ID NOS:1-4 in a Markush-type grouping, the Sequence Election Requirement presents each of SEQ ID NOS:1-4 as unrelated, patentably distinct sequences, thus introducing a contradiction into the prosecution history. Such contradictions can potentially diminish the value of any patent that may issue from the instant application. For example, since Applicants are required to elect a Group (and a single sequence) for prosecution on the merits, one reading the prosecution history may incorrectly assume that Applicants admit that the biopolymer markers of SEQ ID NOS:1-4 are separate and distinct inventions.

Request for Rejoining of Claims

Considering that claims 39-46 are limited to the use of SEQ ID NO:3 a search of these claims would encompass this specific peptide. The instant application is related in claim format to several other applications, both pending and issued, of which serial number 09/846,352 is exemplary. In an effort to maintain equivalent scope in all of these applications, Applicants respectfully request that the Examiner consider rejoining claims 39-46 in the instant application, which are currently drawn to non-elected Groups, with claim 1 of the elected Group under the decision in *In re Ochiai* (MPEP 2116.01), upon the Examiner's determination that claim 1 of the elected invention is allowable and in light of the overlapping search. If the biopolymer marker peptide of SEQ ID NO:3 is found to be novel, methods and kits limited to its use should also be found novel.

Information Disclosure Statement

The Examiner has pointed out that the listing of references in the specification is not a proper Information Disclosure Statement. 37 CFR 1.98(b) requires a list of all patents, publications or other information submitted for consideration by the Office, and MPEP 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a

separate paper." Thus, the Examiner indicates that unless the Examiner on PTO-892 form or Applicant on PTO-1449 form has cited the references they have not been considered.

The Examiner indicates that the Information Disclosure Statement filed on March 22, 2002 has been considered as to the merits prior to the first action.

The references cited within the specification but not included in the above-mentioned Information Disclosure Statement provide general information relating to background information and/or the state of the art, but were not deemed pertinent to the patentability of the claimed invention.

Oath/Declaration

A new oath or declaration has been required by the Examiner because while the original oath filed on March 6, 2002 contains the signature of Dr. John Marshall (inventor 2), the date of signature is omitted.

Applicants are currently in the process of preparing a new oath and will forward such oath to the Examiner as soon as it is completed and properly executed.

Objections to the Specification

The Examiner notes the use of trademarks in the application

(i.e. SEPHAROSE at page 41, lines 6 and 7 and TRITON at page 42, line 14) which should be capitalized wherever they appear and be accompanied by the generic terminology. The Examiner further notes that although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Applicants have amended the specification at pages 40-45 to properly identify trademark names (SEPHAROSE, TRITON, TRIS and EPPENDORF).

The Examiner points out guidelines for the proper language and format of an abstract of a patent application and objects to the abstract of the instant application as it recites the legal phraseology "said".

The abstract of the instant application has been amended herein to remove the legal phraseology "said".

Applicants have now addressed all of the Examiner's objections and respectfully request that the objections to the specification be withdrawn.

Rejection under 35 USC 112, second paragraph

Claim 1, as presented on December 10, 2004, stands rejected under 35 USC 112, second paragraph, as being indefinite for

allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner asserts that claim 1 is vague and indefinite because the biopolymer is "diagnostic" for insulin resistance. "Diagnostic" reads on not only the detection of the disease but also the analysis of the cause or nature of the disease. It is not clear how the biopolymer marker will analyze the cause or nature of insulin resistance. Applicants' intended meaning of "diagnostic" is not defined by the claims or the specification. The specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The Examiner suggests that the claim merely recite "detection of" insulin resistance in order to obviate this rejection.

Applicants respectfully disagree with the Examiner's assertions.

The term "diagnostic" refers to the identification of a property or characteristic, usually regarding health of an individual, such as, identifying a disease linked with the property or characteristic. It is clear from the multiple disclosures in the instant specification that the term "diagnostic" or "diagnose" refers to the identification of a disease; see, for example, page 5, lines 12-20; page 31, lines 19-22; page 32, lines 7-10; page 36,

lines 9-12; page 48, lines 10-12; page 52, lines 11-14 and page 53, lines 2-9. According to the web site dictionary. com; the term "diagnostic" relates to or refers to use in diagnosis; use in serving to identify a particular disease or to a symptom or a distinguishing feature; and/or use in serving as supporting evidence in a diagnosis (see attached definition as accessed from the internet; reference 1).

Neither the art nor the specification suggests that "diagnostic" refers to anything other than identification of a disease. Thus, Applicants respectfully submit that the Examiner has no basis for asserting that the term "diagnostic" reads on not only the detection of the disease but also the analysis of the cause or nature of the disease.

However, in the interest of compact, efficient prosecution, Applicants have amended the claim to remove the term "diagnostic".

Accordingly, Applicants have now clarified the metes and bounds of the claims and respectfully request that the above-discussed rejection under 35 USC 112, second paragraph be withdrawn.

Rejection under 35 USC 101

Claim 1, as presented on December 10, 2004, stands rejected under 35 USC 101 because the claimed invention allegedly is not

supported by a either a specific, substantial, credible or asserted utility or a well-established utility.

Applicants respectfully disagree with the Examiner's contention and assert that the claimed invention has both a specific and a well-established utility.

The Examiner asserts that applicants have disclosed in the specification that SEQ ID NO:3 is measurable in patients with insulin resistance but is undetectable in normal patients.

Applicants respectfully assert that this statement made by the Examiner is incorrect.

Page 46 of the instant specification indicates that practice of the disclosed procedures identifies the peptide of SEQ ID NO:3 as related to insulin resistance. Contrary to the Examiner's assertion, SEQ ID NO:3 is measurable in normal patients but undetectable in patients with a history of insulin resistance or diabetes; see Figure 1, wherein the fibronectin precursor is evident in lanes 7-9 (gel is read from the left) which contain samples obtained from patients determined to be normal with regard to insulin resistance.

Additionally, the Examiner asserts that the disclosure appears to require not only SEQ ID NO:3 but a combination of SEQ ID NOS:1-4 for the identification of insulin resistance.

Applicants respectfully assert that this statement made by the

Examiner is also incorrect.

At page 46, lines 10-18 of the instant specification as originally filed, SEQ ID NOS:1-4 are identified as peptides which are related to insulin resistance. No where does the specification indicate that a combination of markers (SEQ ID NOS:1-4) is a requirement for the identification of insulin resistance through use of the disclosed methods. Contrary to the Examiner's assertion, each of the disclosed peptides (SEQ ID NOS:1-4) has the ability to be independently related to insulin resistance.

At page 9 of the Office Action mailed on January 12, 2005, the Examiner asserts that SEQ ID NO:3 does not appear to be a marker for insulin resistance.

Applicants respectfully disagree with the Examiner's line of reasoning and assert that SEQ ID NO:3 is useful for diagnosis and treatment of insulin resistance since it was found to evidence a link to insulin resistance (an "asserted" utility).

The Examiner is reminded that an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement under 35 USC 101 (see MPEP 2107.02 III A). Thus, the requirements of 35 USC 101 are met solely by Applicants above assertion regarding the use of the claimed peptide (SEQ ID NO:3).

Furthermore, Applicants' statement of an asserted utility also

constitutes a specific and substantial utility that is supported by the specification as originally filed (see page 1, lines 5-13; page 35, lines 14-18; page 46, lines 10-18 and Figures 1 and 4).

The claimed peptide (SEQ ID NO:3) does not evidence a link to a myriad of unspecified diseases but rather evidences a link to a specific disease, insulin resistance, thus the invention has a specific utility.

Furthermore, advances in diagnosis and treatment of insulin resistance are highly desirable considering that insulin resistance is often a prelude to the development of clinical diabetes. The claimed peptide (SEQ ID NO:3) represents an advance in research regarding insulin resistance and diabetes; a "real-world" use. Thus, the claimed peptide (SEQ ID NO:3) additionally has a substantial utility.

It has been established that where an applicant has specifically asserted that an invention has a particular utility, the assertion cannot be simply dismissed by Office personnel as being "wrong", even when there may be a reason to believe that the assertion is not entirely accurate (see MPEP 2107.02 III B).

Although the Examiner should regard Applicants' statement of asserted utility sufficient to satisfy the requirements of 35 USC 101, the Examiner lists several reasons which allegedly support her argument that the claimed invention has no utility.

First, the Examiner asserts that the figures do not clearly identify SEQ ID NO:3 or its ability to determine normal patients as well as insulin resistance patients.

Applicants respectfully assert that the Examiner's statement is incorrect.

SEQ ID NO:3 is identified as a fibronectin precursor peptide having a molecular weight of about 1819 daltons at page 46, lines 10-18 of the originally filed specification. Figure 4 shows the characteristic profile obtained by mass spectrometry of an ion of about 1819 daltons (SEQ ID NO:3). Band #1 as seen in Figure 1 is identified as fibronectin precursor. Thus, contrary to the Examiner's contention, Figure 1 does clearly identify SEQ ID NO:3.

Furthermore, lanes 7-9 (as read from the left) of the gel pictured in Figure 1 show the presence of Band #1 in serum samples obtained from patients who were normal (with respect to insulin resistance and diabetes). This Band #1 is not evident in serum samples obtained from patients with a history of insulin resistance, Type I diabetes or Type II diabetes. Thus, again contrary to the Examiner's contention, Figure 1 does demonstrate an ability to determine patients exhibiting insulin resistance from patients who do not exhibit insulin resistance (normal).

The Examiner asserts that no clear difference in up and down regulation of the marker can be determined; and thus SEQ ID NO:3

does not appear to be a marker for insulin resistance.

Applicants respectfully disagree with the Examiner's assertions.

The gel in Figure 1 clearly shows the presence of Band #1 in all three samples obtained from patients who were determined to be normal with regard to insulin resistance and diabetes. The gel of Figure 1 also clearly shows the absence of Band #1 in samples obtained from patients having a history of insulin resistance or diabetes. Thus, contrary to the Examiner's assertion, a clear difference in up and down regulation of the marker can be determined from the data presented in the instant specification.

In the medical arts proteins found to be differentially expressed between "disease" and "normal" are frequently identified as potential targets for diagnostics and/or therapeutics. For example, when a peptide is identified in a body fluid sample from an Alzheimer's patient, it is immediately recognized as a potential diagnostic marker, even if the involvement of the peptide in the pathology of Alzheimer's disease is unknown. One of skill in the art would be familiar with this practice since it has been known in the art since at least 1992. See attached abstract of Gunnersen et al. (Proceedings of the National Academy of Science USA 89(24):11949-11953 1992; reference 2) in which the detection of glutamine synthetase in the cerebrospinal fluid of Alzheimer's

disease patients lead to the suggestion of glutamine synthetase as a potential diagnostic biochemical marker. Thus, when one of skill in the art observes the claimed peptide differentially expressed between insulin resistance/diabetes patients and normal patients; one of skill in the art would connect the peptide with potential diagnostics and/or therapeutics for insulin resistance and/or diabetes and would immediately appreciate why applicants regard the claimed peptide (SEQ ID NO:3) as useful. Thus, Applicants respectfully submit that the utility of the claimed peptide (SEQ ID NO:3) is well-established.

Insulin resistance and vascular complications are well known components of diabetic pathology (see attached abstracts of Ramarao et al. Drugs Today (Barc) 35 (12):895-911 1999; reference 3 and Yudkin et al. Diabetologia 43(9):1099 2000; reference 4). Furthermore, fibronectin is a known marker of endothelial and vascular dysfunction (see Yudkin et al.; reference 4).

At page 46, lines 10-18 of the instant specification as originally filed, SEQ ID NO:3 is identified as a fibronectin precursor peptide. The instant inventors have hypothesized that fibronectin is damaged or fragmented due to vascular damage during the process of insulin resistance and thus may represent a potential marker for the early detection of diabetes. One of skill in the art, considering that fibronectin is a known marker for

vascular damage and also considering the known vascular complications associated with insulin resistance, would find such a hypothesis reasonable.

Therefore, one of skill in the art would recognize the linkage between insulin resistance, vascular damage and SEQ ID NO:3 and thus would also find the suggestion of SEQ ID NO:3 as a marker for insulin resistance entirely reasonable.

Accordingly, Applicants assert that the claimed invention has both a specific and a well-established utility and respectfully request that this rejection under 35 USC 101 now be withdrawn.

Rejection under 35 USC 112, first paragraph

Claim 1, as presented on December 10, 2004, stands rejected under 35 USC 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner asserts that the claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner makes the following assertions:

Claim 1 is directed to a biopolymer consisting of SEQ ID NO:3 diagnostic for insulin resistance. The Examiner contends that the specification does not support this assertion. The specification

(in particular page 46) and the figures do not definitively correlate the claimed marker consisting of SEQ ID NO:3 to insulin resistance. The specification recites that the biopolymer consisting of SEQ ID NO:3 was found in the serum of patients suffering from insulin resistance on page 46, but the specification does not contain any data supporting this contention and the figures do not identify SEQ ID NO:3 as a definitive marker for insulin resistance. Therefore, it is unclear how SEQ ID NO:3 was identified as "notable" or how it was deemed "evidentiary" of a disease state. There is nothing in the disclosure that would enable one to choose SEQ ID NO:3 as a notable sequence among an infinite number of possible proteins or peptides present in a patient sample.

Applicants respectfully disagree with all of the Examiner's assertions.

Although Applicants believe that the instant specification, as originally filed, fully supports the claim that an isolated peptide consisting of SEQ ID NO:3 is diagnostic for insulin resistance, in the interest of compact, efficient prosecution, Applicants have removed the term "diagnostic" from the claims and note that the isolated peptide consisting of SEQ ID NO:3 is linked to insulin resistance.

According to the web site dictionary.com the term "linked"

refers to the condition of being associated with or connected to (see attached document as accessed from the internet; reference 5). The instant specification fully supports a connection and/or an association of the claimed peptide with insulin resistance. The instant specification states at page 35, lines 14-18 that an objective of the invention is to evaluate samples containing a plurality of biopolymers for the presence of disease specific biopolymer marker sequences which evidence a link to at least one specific disease state.

The "test of enablement" is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the prior art without undue experimentation (see MPEP 2164.01).

Furthermore, the decision in *In re Brandstadter* (179 USPQ 286; MPEP 2164.05) has established that the evidence provided by applicant (to overcome an enablement rejection) need not be conclusive but merely convincing to one of skill in the art.

Applicants respectfully submit that the instant specification provides sufficient evidence to convince one of skill in the art that the claimed peptide (SEQ ID NO:3) is linked and/or associated with insulin resistance.

Claim 1 has been amended to specifically recite an isolated peptide consisting of SEQ ID NO:3, a peptide which the instant

specification identifies as related to insulin resistance. Claim 1, as amended herein, does not recite that the claimed isolated peptide is diagnostic for insulin resistance, nor does it recite that the claimed isolated peptide is related to insulin resistance, even though Applicants believe that the specification, as originally filed, fully supports both of these recitations. Furthermore, the phrase "consisting of" is closed language and excludes any element, step or ingredient not specified in the claims (see MPEP 2111.03). Thus, the scope of claim 1 is limited to this specific peptide (SEQ ID NO:3).

At page 46, lines 10-18 of the specification as originally filed, SEQ ID NO:3 is identified as a fibronectin precursor peptide having a molecular weight of about 1819 daltons. The description of Figure 4 at page 37 indicates that the spectra depicted in the figure is that of ion 1819. Ion 1819 is known to be SEQ ID NO:3 based upon the information disclosed at page 46 of the instant specification. The spectra shown in Figure 4 was obtained from Band #1 (resolved from a sample obtained from a patient determined to be normal with regard to insulin resistance and diabetes) as shown in the gel of Figure 1. The descriptions of the figures have been amended to clarify that the data shown in the figures is representative of the claimed and/or disclosed peptides.

Figure 1 demonstrates that the biopolymer marker peptide (Band

#1; SEQ ID NO:3) is present in body fluid samples obtained from patients determined to be normal with regard to insulin resistance and diabetes, but is not present in body fluid samples obtained from patients having a history of insulin resistance or diabetes (contrary to the Examiner's understanding of the claimed peptide being found in the serum of patients suffering from insulin resistance). Thus, a difference is seen between two comparable samples, suggesting that the differentially expressed peptide is linked to insulin resistance.

The specification, as originally filed, does provide a precise protocol on how to analyze the data obtained from the disclosed method. Page 25, line 16 to page 26, line 2 of the instant specification discloses a general outline of how to analyze the data obtained by carrying out the disclosed methods. Page 26, lines 6-13 of the instant specification further describes how samples were compared to develop data and indicates how biopolymer marker peptides were selected as notable sequences. This passage of the instant specification also discloses how certain peptides were selected from a plurality of molecules found within a sample and how peptides were deemed evidentiary of a disease state. Page 5, lines 12-20 also describes how biopolymer markers are evaluated according to the methods of the instant invention. Page 47, lines 3-10 of the instant specification clearly states the steps of the

invention include obtaining a sample from a patient and conducting an MS analysis (mass spectrometry) on the sample. Mass spectrometry is commonly practiced and one of skill in the art would know how to analyze and obtain information from mass spectrometry profiles. It is clear that the data presented in the instant specification was obtained by carrying out mass spectrometry. Thus, Applicants assert that the specification, as originally filed, provides a precise protocol on how to analyze the data obtained by the disclosed protocol.

Additionally, Applicants respectfully submit that such protocols are common practice in the field of proteomics. For example, Lubec et al. (see attached abstract Journal Neural Transmission Supplement 57:161-177 1999; reference 6) disclose an experiment in which proteomic techniques, specifically electrophoresis and mass spectrometry, were carried out to detect differences in protein expression between Down's syndrome patients, Alzheimer's patients and "normal" control patients. In a manner similar to that of the instant inventors, Lubec et al. analyzed the increase and/or decrease in expression of a particular protein (DRP-2) when hypothesizing about the neuropathological findings in Alzheimer's disease and Down's syndrome.

Furthermore, Applicants assert that those of skill in the art are both highly knowledgeable and skilled and it is obvious that

no undue experimentation would be required for a skilled artisan to follow any of the electrophoretic, chromatographic and mass spectrometric protocols presented in the instant specification in order to use the claimed invention. One of skill in the art would be able to view a gel, such as that shown in Figure 1 from which the claimed peptide was identified (SEQ ID NO:3), and recognize a difference between two comparable samples (disease state vs. non-disease state) and further recognize that the peptides present within the gel are differentially expressed between the two sample types.

Figure 1 is a photograph of a gel showing the results of HiQ column chromatography as carried out with a set of 8 samples (lanes 2-9 of the gel as read from the left); lane 2 contains a serum sample obtained from a patient with a history of Type I diabetes; lanes 3 and 4 contain serum samples from patients with a history of insulin resistance; lanes 5 and 6 contain serum samples from patients having a history of Type II diabetes and lanes 7-9 contain serum samples from patients determined to be normal with regard to insulin resistance and diabetes. Lane 1 was reserved for low molecular weight standard markers and lane 10 was reserved for high molecular weight standard markers. Lanes 7-9, containing serum samples from normal patients, display Band #1, a fibronectin precursor peptide. Band #1 is not evident in any of the lanes

containing diabetes and insulin resistance samples.

The data presented in the figures, derived from the working examples, discloses that the claimed peptide (SEQ ID NO:3) is differentially expressed between insulin resistance/diabetes and a "normal" physiological state, thus it can be reasonably predicted that such peptide is linked to insulin resistance. Furthermore, the figures identify SEQ ID NO:3 and the specification discloses how such a sequence was identified as a notable sequence in relation to insulin resistance.

Thus, Applicants contend a skilled practitioner would find that the data presented in the instant specification is convincing with regard to a link between the claimed biopolymer marker peptide (SEQ ID NO:3) and insulin resistance.

Considering the above comments, it is clear that both the specification and the prior art disclose how to make and use the instant invention. Accordingly, Applicants respectfully contend that the instant invention satisfies the "test for enablement" since one skilled in the art could make or use the invention from the disclosures in the specification coupled with information known in the prior art without undue experimentation.

The Examiner makes a series of assertions regarding the enablement of subject matter which is not claimed, including the following:

The Examiner asserts that there is no correlation between the procedure for screening samples from patients suspected of having a variety of different diseases, the presence/absence of SEQ ID NO:3; and the determination, prediction, assessment of insulin resistance. There is no disclosure enabling the use of the biopolymer marker with regard to regulating the presence or absence of said marker. The disclosure is lacking any teaching for how the identified sequence will be utilized to identify therapeutic avenues and regulation of a disease state. There is no disclosure designating how the sequence could be utilized therein, enabling one of ordinary skill in the art to use the sequence in the diagnostic method.

The Examiner is reminded that all questions of enablement should be evaluated against the claimed subject matter and the focus of the examination inquiry should be a question of whether everything within the scope of the claims is enabled (see MPEP 2164.08).

Accordingly, an Applicant is not required to enable material which is not claimed. The pending claims do not recite any disease state other than insulin resistance, nor do the pending claims recite identification of therapeutic avenues or methods of regulating the sequence or a disease state. Thus, no teachings regarding these issues are necessary in order to provide evidence

for enablement of the pending claims.

The Examiner asserts that Applicants have not set forth any supporting evidence that suggests that any of the sequences (in particular SEQ ID NO:3) are unique molecular markers for insulin resistance or any other disease and the prior art teaches that disease markers are highly unpredictable and require extensive experimentation. The Examiner further asserts that Applicants merely suggest that SEQ ID NO:3 is a marker for insulin resistance; which is allegedly contrary to the teachings of Foss et al. (Journal of Internal Medicine 252:155-163 2002) which discloses that the levels of fibrinogen and fibronectin were not useful markers in detecting insulin resistance.

The guidelines for a "test of enablement" indicate that if a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 USC 112, is satisfied (see MPEP 2164.01(c)).

Additionally, it has been established that the mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it (see MPEP 2164.02).

A copy of the article cited by the Examiner (Foss et al. Journal of Internal Medicine 252(2):155-263 2002) was not included

with the Office Action mailed on January 12, 2005. Applicants respectfully request that a copy of said article be included with the next Office communication from the Examiner to Applicants.

Apparently, the Examiner believes that the Foss article is relevant to the enablement of the instant invention as currently claimed. The Examiner contends that Foss et al. teach that the levels of fibrinogen and fibronectin were not useful markers in detecting insulin resistance.

Applicants respectfully disagree with the Examiner's interpretation of the study by Foss et al.

One of the objectives of Foss et al. was to examine whether levels of fibronectin were related to a parental history of Type II diabetes (see attached abstract of Foss et al. Journal of Internal Medicine 252(2):155-263 2002; reference 7). Foss et al. found that the levels of fibronectin were not influenced by a parental history of Type II diabetes.

In contrast to the study of Foss et al., the instant inventors compare the presence of fibronectin in a disease-state versus a physiologically normal state; thus the study of Foss et al. (comparison of fibronectin levels in parental history) is not analogous to the study of the instant inventors.

Accordingly, Applicants respectfully submit that the article of Foss et al. is not relevant to the enablement of the instant

invention.

Applicants assert that SEQ ID NO:3 is linked to insulin resistance, however, do not claim that SEQ ID NO:3 is a unique marker for any particular disease or condition.

Although the prior art does not specifically recognize that the claimed SEQ ID NO:3 is related to insulin resistance, it does recognize that when a peptide is identified in a body fluid sample from an Alzheimer's patient or appears to be differentially expressed between an Alzheimer's disease patient and a "normal" patient, it is immediately recognized as a potential diagnostic marker, even if the involvement of the peptide in the pathology of Alzheimer's disease is unknown. One of skill in the art would be familiar with this practice since it has been known in the art since at least 1992. See attached abstract of Gunnersen et al. (Proceedings of the National Academy of Science USA 89(24):11949-11953 1992; reference 2) in which the detection of glutamine synthetase in the cerebrospinal fluid of Alzheimer's disease patients lead to the suggestion of glutamine synthetase as a potential diagnostic biochemical marker for Alzheimer's disease. When one of skill in the art observes differential expression of the claimed peptide between diseased patients and non-diseased patients; one of skill in the art would connect this peptide with potential diagnostic and/or therapeutics for insulin resistance.

Thus, Applicants respectfully submit that since the specification demonstrates a link between the claimed peptide (SEQ ID NO:3) and insulin resistance and that this link connotes the use of the claimed peptide in potential diagnostics and/or therapeutics of insulin resistance, the requirement of "how to use" under 35 USC 112, first paragraph is satisfied.

Furthermore, Applicants respectfully submit that one of ordinary skill in the art would find the suggestion of a link between the claimed peptide (SEQ ID NO:3) and insulin resistance to be reasonable.

Insulin resistance and vascular complications are well known components of diabetic pathology (see attached abstracts of Ramarao et al. Drugs Today (Barc) 35 (12):895-911 1999; reference 3 and Yudkin et al. Diabetologia 43(9):1099 2000; reference 4). Furthermore, fibronectin is a known marker of endothelial and vascular dysfunction (see Yudkin et al.; reference 4).

At page 46, lines 10-18 of the instant specification as originally filed, SEQ ID NO:3 is identified as a fibronectin precursor peptide. The instant inventors have hypothesized that fibronectin is damaged or fragmented due to vascular damage during the process of insulin resistance and thus may represent a potential marker for the early detection of diabetes. One of skill in the art, considering that fibronectin is a known marker for

vascular damage and also considering the known vascular complications associated with insulin resistance, would find

Therefore, one of skill in the art would recognize the linkage between insulin resistance, vascular damage and SEQ ID NO:3 and thus would also find the suggestion of SEQ ID NO:3 as a marker for insulin resistance entirely reasonable.

The Examiner cites two articles; Tascilar *et al.* (Annals of Oncology 10, Supplement 4:S107-S110 1999) and Tockman *et al.* (Cancer Research 52:2711s-2718s 1992) which are allegedly relevant to the instant invention.

According to the Examiner, Tascilar *et al.* is an article published in an oncogenic journal reporting on diagnostic methods in the realm of disease states. The Examiner appears to have drawn a direct parallel between the diagnostic methods reported by Tascilar *et al.* and the diagnostic methods of the instant invention. The Examiner then cites two fragmented quotations from Tascilar *et al.* "...these tests should be interpreted with caution..." and "the genetic changes found in sources other than the pancreas itself (blood, stool) should be evaluated prudently". The Examiner appears to be commenting on the predictability of molecular-based assays.

Applicants respectfully disagree with the Examiner's reliance on the article by Tascilar et al.

Applicants assert that the claimed peptide (SEQ ID NO:3) is linked to insulin resistance; a statement which is enabled by the description of methods as set forth in the specification and by data presented in Figures 1 and 4. Thus, applicants respectfully submit that the claimed method involves a simple observation of the presence of SEQ ID NO:3 (as shown in Figure 1) and does not require any other evaluation of genetic changes in the organism in which the sequence is observed.

Furthermore, the study of Tascilar et al. is concerned with the evaluation of samples for genetic mutations (K-ras and p53 mutations) for early detection of pancreatic cancer (see attached abstract of Tascilar et al. Annals of Oncology 10, Supplement 4:S107-S110 1999; reference 8). It appears that Tascilar et al. suggest that protein markers may be useful for early detection of pancreatic cancer; however there does not seem to be any other reference to protein markers, thus the study of the instant inventors (drawn to protein markers and not to genetic markers) is not analogous to the study of Tascilar et al.

Accordingly, Applicants respectfully submit that the Tascilar *et al.* article is not relevant to the instant invention.

Similarly, the Examiner cites another article, Tockman *et al* (Cancer Research Supplement 52:2711s-2718s 1992) which is deemed to teach conditions necessary for a suspected cancer biomarker

(intermediate end point marker) to have efficacy and success in a clinical application. The reference is drawn to biomarkers for early lung cancer detection, however the basic principles are applicable to other oncogenic disorders, according to the Examiner. Tockman *et al* is deemed to teach that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials. Early stage markers of carcinogenesis have clear biological plausiblity as markers of pre-clinical cancer if validated to a known cancer outcome. Tockman *et al* is deemed to teach that the essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical disease and link those marker results with histological confirmation of disease.

Applicants respectfully disagree with the Examiner's reliance on the article by Tockman et al.

The Tockman *et al* article is concerned with early detection of lung cancer biomarkers and apparently does not discuss biomarkers for insulin resistance or diabetes.

Tockman et al. link several biopolymer markers to lung cancer in a manner analogous to that of the instant specification. Tockman

et al. state at page 2712s, left column:

"A functional membrane-associated bombesin receptor recently has been isolated from human small cell lung carcinoma (NCI-H345) cells (23), and bombesin-like peptides have been found in the bronchial lavage fluid of asymptomatic cigarette smokers (24). Thus markers of growth factor expression, insofar as they reflect oncogene activation, may also hold promise for the detection of early (preneoplastic) lung cancer."

From this statement, it is clearly evident that Tockman et al. link bombesin with small cell lung cancer and associate it with potential diagnostics for small cell lung cancer. It does not appear that bombesin was "validated" and/or subjected to any "criteria" prior to this association.

Additionally, Tockman et al. state at page 2713s, left column:

"Evidence of a transformed genome, by expression of tumor-associated antigens, oncofetal growth factors, or specific chromosomal deletions has clear biological plausibility as a marker of preclinical lung cancer."

From this statement, it appears that Tockman et al. believe that the expression of certain proteins provides evidence of a transformed genome and since this transformed genome is associated with lung cancer, it is reasonable to believe that these certain proteins are potential markers.

Such parallel reasoning between Tockman et al. and the instant specification, further supports Applicants contention that one of ordinary skill in the art would not have any difficulty seeing a link between the claimed biopolymer marker peptide (SEQ ID NO:3) and insulin resistance.

It is noted that in chemical and biotechnical applications, evidence actually submitted to the FDA to obtain approval for clinical trials may be submitted to support enablement of an invention. However, considerations made by the FDA for approving clinical trials are different from those made by the PTO in determining whether a claim is enabled (see *Scott v. Finney* 32 USPQ 2d 1115 and MPEP 2164.05)

The Examiner is reminded that the considerations made by the PTO involving clinical trials are less stringent than the considerations made by the FDA. Evidence presented by applicant to provide enablement of an invention need only be convincing to one of skill in the art and not conclusive. Thus, Applicants respectfully submit that compliance with the "criteria" of Tockman et al. is not necessary in order to show that the instant invention is enabled.

In conclusion, Applicants claim that the differential expression of SEQ ID NO:3 between insulin resistance/diabetes patients and patients determined to be normal with regard to

insulin resistance and diabetes evidences a link between the claimed peptide (SEQ ID NO:3) and insulin resistance; a statement which is enabled by the instant specification, as evidenced by the arguments presented herein. Applicants assert that one of ordinary skill in the art when reviewing the instant specification, given the level of knowledge and skill in the art, would recognize the link between the claimed biopolymer marker (SEQ ID NO:3) and insulin resistance and would further recognize how to use the claimed peptide (SEQ ID NO:3) as a marker for insulin resistance. Thus, Applicants respectfully request that this rejection under 35 USC 112, first paragraph now be withdrawn.

CONCLUSION

In light of the foregoing remarks, amendments to the specification and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,

Katharine F Davis

Katharine Davis
Registration # 51,598

McHale & Slavin, P.A.
2855 PGA Boulevard
Palm Beach Gardens, FL 33410
(561) 625-6575 (Voice)
(561) 625-6572 (Fax)

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